Targeting Host Pathways to Block HSV-1 at the Cornea

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Most antiviral strategies act selectively on the virus replication machinery over that of the host, with the difference between host toxicity and antiviral activity determining efficacy. This can involve preferential binding to, or activation by, viral proteins over those of the host. The anti-HSV (herpes simplex virus) drug acyclovir (ACV) is a classic example that employs both strategies: ACV is activated only in HSV-infected cells by the initial phosphorylation by the herpes simplex virus type 1 (HSV-1)-specified thymidine kinase, and then the triphosphate form of ACV is preferentially used by the HSV-1-encoded polymerase over that of the host, resulting in DNA chain termination. While effective, viral genetic changes can result in modified structure or expression of the viral proteins involved, resulting in the development of antiviral resistance.

One well-proposed strategy to circumvent antiviral resistance acts is to target host cellular pathways that are required by viruses such as HSV for their replication. However, development of such strategies has been slow, partly due to the obvious complication that host cell pathway inhibition will change the host cell environment and induce cellular toxicity. The key is to identify those cellular pathways that are essential for HSV replication but that, when inhibited, have little effect on the host cell outcome.

Alekseev et al. report that topical application of an inhibitor of the ataxia telangiectasia mutated (ATM) kinase, an apical host cell kinase with a key role in the activation of the host DNA damage response, can effectively suppress viral replication of HSV-1 in both in vitro and ex vivo and, excitingly, in in vivo models of corneal infection. It is known that HSV-1 hijacks this pathway for its replication, and indeed, the study shows high ATM activation by HSV-1 in the infected corneal cell. However, crucial to the field is the demonstration that inhibition blocks not only viral replication in vivo, but also the development of ocular disease in a mouse model of stromal keratitis. Moreover, the inhibitor also complemented the effectiveness of ACV treatment and was effective against ACV-resistant HSV-1. Remarkably, the inhibition of ATM appears to have few consequences to the health of the cornea and its cells. This establishes a basis for the inhibition of ATM as lead target for antiviral treatment of HSV-1 corneal infections.

Reference


DOI: 10.1167/iovs.14-13879

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